Relationship Between Peak Troponin Values and Long-Term Ischemic Events Among Medically Managed Patients With Acute Coronary Syndromes

Goldstein, Sarah A ; Newby, L Kristin ; Cyr, Derek D ; Neely, Megan ; Lüscher, Thomas F ; Brown, Eileen B ; White, Harvey D ; Ohman, E Magnus ; Roe, Matthew T ; Hamm, Christian W

Abstract: BACKGROUND The relationship between troponin level and outcomes among patients with non-ST-segment elevation ACS is established, but the relationship of troponin level with long-term outcomes among medically managed non-ST-segment elevation ACS patients receiving contemporary antiplatelet therapy is inadequately defined. METHODS AND RESULTS In 6763 medically managed non-ST-segment elevation ACS patients randomized in TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) (prasugrel versus clopidogrel), we examined relationships between categories of peak troponin/upper limit of normal (ULN) ratio within 48 hours of the index ACS event (4.5 days before randomization) and 30-month outcomes (cardiovascular death, myocardial infarction, or stroke; cardiovascular death or myocardial infarction; and all-cause death). Patients with peak troponin levels <1×ULN were younger, were more often women, and had lower GRACE risk scores than those in other troponin groups. Those with ratios 5×ULN were more frequently smokers but less often had prior myocardial infarction or percutaneous coronary intervention. Diabetes mellitus prevalence, body mass index, serum creatinine, and hemoglobin were similar across groups. For all end points, statistically significant differences in 30-month event rates were observed between peak troponin categories. The relationship was linear for 30-month mortality (<1×ULN, n=1849 [6.2%]; 1 to <3×ULN, n=1203 [9.6%]; 3 to <5×ULN, n=581 [10.8%]; and 5×ULN, n=3405 [12.8%]) but plateaued for composite end points beyond peak troponin values 3×ULN. There was no statistically significant heterogeneity in treatment effect by peak troponin ratio for any end point. CONCLUSIONS Among medically managed non-ST-segment elevation ACS patients selected for medical management, there was a graded relationship between increasing peak troponin and long-term ischemic events but no heterogeneity of treatment effect for prasugrel versus clopidogrel according to peak troponin. CLINICAL TRIAL REGISTRATION URL: http://www.clinicaltrials.gov. Unique identifier: NCT00699998.

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ORIGINAL RESEARCH

Relationship Between Peak Troponin Values and Long-Term Ischemic Events Among Medically Managed Patients With Acute Coronary Syndromes

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***Background*—**The relationship between troponin level and outcomes among patients with non-ST-segment elevation ACS is established, but the relationship of troponin level with long-term outcomes among medically managed non-ST-segment elevation ACS patients receiving contemporary antiplatelet therapy is inadequately defined.

***Methods and Results*—**In 6763 medically managed non-ST-segment elevation ACS patients randomized in TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) (prasugrel versus clopidogrel), we examined relationships between categories of peak troponin/upper limit of normal (ULN) ratio within 48 hours of the index ACS event (≈4.5 days before randomization) and 30-month outcomes (cardiovascular death, myocardial infarction, or stroke; cardiovascular death or myocardial infarction; and all-cause death). Patients with peak troponin levels <1×ULN were younger, were more often women, and had lower GRACE risk scores than those in other troponin groups. Those with ratios ≥5×ULN were more frequently smokers but less often had prior myocardial infarction or percutaneous coronary intervention. Diabetes mellitus prevalence, body mass index, serum creatinine, and hemoglobin were similar across groups. For all end points, statistically significant differences in 30-month event rates were observed between peak troponin categories. The relationship was linear for 30-month mortality (<1×ULN, n=1849 [6.2%]; 1 to <3×ULN, n=1203 [9.6%]; 3 to <5×ULN, n=581 [10.8%]; and ≥5×ULN, n=3405 [12.8%]) but plateaued for composite end points beyond peak troponin values ≥3×ULN. There was no statistically significant heterogeneity in treatment effect by peak troponin ratio for any end point.

***Conclusions*—**Among medically managed non-ST-segment elevation ACS patients selected for medical management, there was a graded relationship between increasing peak troponin and long-term ischemic events but no heterogeneity of treatment effect for prasugrel versus clopidogrel according to peak troponin.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00699998. **(*J Am Heart Assoc*. 2017;6: e005334. DOI:10.1161/JAHA.116.005334.)**

Key Words: acute coronary syndromes • myocardial infarction • risk stratification • troponin

The relationship between baseline levels of troponin or creatine kinase-MB and outcomes among patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS) is established.[1] This relationship has not been well studied in medically managed NSTE ACS populations in the era of modern antithrombotic therapy that includes systematic use of more potent P2Y12 inhibition as a component of dual antiplatelet therapy. In addition, whether the effect of treatment with a more potent P2Y12 antagonist (eg, prasugrel versus clopidogrel) is influenced by degree of biomarker elevation, particularly among medically managed patients, is unknown. Although the relationship of troponin

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Accompanying Data S1, Tables S1 through S6 and Figures S1, S2 are available at http://jaha.ahajournals.org/content/6/4/e005334/DC1/embed/inline-supplementary-material-1.pdf

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elevation at baseline with outcome is strong over the first 30 days post-ACS, it becomes weaker over longer durations of follow-up.[2,3] The TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial database provided the opportunity to explore these important issues in a medically managed NSTE ACS population treated with long-term dual antiplatelet therapy.

In a substudy of TRILOGY ACS, the Platelet Function Substudy, evaluation of platelet reactivity measured by serial P2Y12 reaction unit (PRU) assessment showed more potent platelet inhibition with prasugrel compared with clopidogrel.[4] There was no relationship between platelet reactivity and ischemic outcomes or differential treatment effect according to platelet reactivity. The relationship between peak troponin level, platelet reactivity, outcomes, and treatment effect has not been explored. The Platelet Function Substudy provided an opportunity to examine these relationships.

Methods

Data Source

The study design and primary results of TRILOGY ACS were previously published.[5] Briefly, TRILOGY ACS was a multinational, double-blind, double-dummy, randomized active controlled trial that compared the effects of prasugrel versus clopidogrel among patients with NSTE ACS who were medically managed without revascularization. The trial was conducted between June 2008 and September 2011 at 966 centers worldwide. The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke at 30-month follow-up. The trial was approved by the institutional review board or ethics committee of all participating sites, and all participants provided written informed consent prior to enrollment. The current analyses were approved by the Duke University Medical Center Institutional Review Board with waiver of informed consent and HIPAA (Health Insurance Portability and Accountability Act of 1996) authorization.

Patient Characteristics and Study Definitions

TRILOGY ACS randomized 9326 patients. For this secondary analysis, we identified 6763 patients (72.5% of the intention-to-treat population) for whom peak troponin (T or I) data were available within 48 hours of the index event. Troponin I was used twice as often as troponin T. Patients were excluded if they had recurrent MI, bypass surgery, or percutaneous coronary intervention between the index event presentation and the reported peak cardiac troponin value. The analysis of platelet function included only patients enrolled in the Platelet Function Substudy who had peak troponin data available (n=1810/2564 [70.6%]).

End Points

Efficacy outcomes of interest in this secondary analysis were the following: (1) 30-month cardiovascular death, MI, or stroke (primary efficacy end point of TRILOGY ACS); (2) 30-month cardiovascular death or MI; (3) 30-month rates of the individual components cardiovascular death, MI, and stroke; and (4) 30-month all-cause death.

Statistical Methods

Because multiple troponin assays were used across the 966 sites in TRILOGY ACS, we normalized site-laboratory-based peak troponin values as a ratio of the site-reported upper limit of normal (ULN) for the assay used. Patients were grouped by categories of peak troponin/ULN ratio ($<1\times$ULN; 1 to $<3\times$ULN; 3 to $<5\times$ULN; $\geq 5\times$ULN). Peak troponin ratios were truncated to the 98th percentile for statistical analysis. For this study, peak troponin was the highest value measured within 48 hours of the index event.

Baseline patient characteristics, including demographics, clinical characteristics, GRACE (Global Registry of Acute Coronary Events) risk score, and concomitant medications at randomization, were summarized according to peak troponin ratio. The GRACE score is a risk-stratification tool developed to estimate the risk of in-hospital and 6-month mortality among all patients hospitalized with ACS. The risk score was created from a risk-prediction model developed using an international ACS registry database.[6] Continuous variables are presented as medians (25th, 75th percentiles), and differences were compared using the Kruskal–Wallis test. Categorical variables are presented as counts (percentages), and differences were compared using the Pearson χ^2 or Fisher exact test if cell frequencies were not sufficient.

For each ischemic outcome, the total number of events and Kaplan–Meier event rates at 30 months after randomization (95% CI) were presented according to peak troponin category. Time-to-event is defined as the time from randomization to the onset of the end point. Time-to-first-event for a composite end point is defined as the time from randomization to the occurrence of the first event of the composite end point. Censoring rules are defined in Tables S1 and S2. Event rates across the follow-up period were compared using the log-rank test.

To examine the relationship between peak troponin level and clinical outcomes, unadjusted and adjusted Cox proportional hazards regression models were developed to test the univariable and multivariable associations of continuous peak troponin ratios with each clinical outcome. TRILOGY ACS

models previously built for each ischemic outcome were used to adjust for baseline characteristics and risk factors. The proportional hazards assumption was checked for each variable, and the linearity assumption was checked for each continuous variable. If the proportional hazards assumption was violated, an interaction of the variable with log-transformed time was included in the model. If the linearity assumption was violated, a linear or restricted cubic spline was used to approximate the nonlinear relationship of the variable with the outcome.[7] In cases where the peak troponin ratio was found to have a nonlinear relationship with a given end point, it was modeled using a linear spline with a knot point at 3.0×ULN, which was determined via numerical simulation across the range of all peak troponin ratios. For further details, please see Table S3. A full description of the TRILOGY ACS adjustment models used in this analysis is provided in Data S1 and Table S4.

The interaction between peak troponin level, study treatment (prasugrel versus clopidogrel), and ischemic outcomes was also computed. Further assessment of this relationship was completed in a subgroup of patients who underwent coronary angiography prior to randomization, eliminating those without angiographically proven coronary disease (lesion causing >50% stenosis).

Baseline characteristics of patients in the Platelet Function Substudy sample were summarized according to peak troponin ratio category. For these patients, the unadjusted and adjusted associations of peak troponin ratio with 30-day PRU values and the interaction with study treatment were evaluated. To gauge the strength of the linear relationship between peak troponin ratio and 30-day PRU values, the Pearson correlation coefficient was computed and the null hypothesis of zero correlation was tested.

All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC). A P value of <0.05 (2-sided) was considered statistically significant. No adjustments were made for multiple comparisons.

Results

Overall Study Sample

Baseline characteristics of the 6763 patients who had sufficient laboratory data reported to determine the peak troponin ratio at 48 hours compared with the 2563 patients who were excluded are provided in Table S5. Baseline characteristics of the 6763 patients included are shown by peak troponin ratio categories in Table 1. Patients with peak troponin ratios <1×ULN were younger, more often women, more often from Central/Eastern Europe, and had lower GRACE risk scores than patients in other troponin groups. Patients with ratios ≥5×ULN more frequently smoked but less often had prior MI or percutaneous coronary intervention. Diabetes mellitus prevalence, body mass index, and hemoglobin were similar across groups. Although there was a statistically significant difference in serum creatinine across troponin groups, absolute differences were small and unlikely to be clinically relevant.

Ischemic Outcomes According to Peak Troponin

Table 2 shows the number of 30-month ischemic outcome events and Kaplan–Meier event rates across peak troponin categories. Figure 1 displays corresponding Kaplan–Meier event rate curves. Trends for increasing event rates with increasing peak troponin ratios were statistically significant for all end points. The relationship was linear for 30-month all-cause mortality but appeared to increase and then plateau at peak troponin ratios ≥3×ULN for the composite end points. The greatest difference in event rates was between peak troponin ratios <1×ULN and any peak troponin ratio ≥1×ULN during early follow-up. Through 30 months, event rates for patients with peak troponin ratios ≥5×ULN were more than twice as high as rates for patients with peak troponin ratios <1×ULN.

Table 3 displays unadjusted and adjusted hazard ratios for 30-month ischemic outcomes per unit increase in peak troponin ratio, modeled as a linear spline. The graphic representation of this relationship for the primary efficacy end point is displayed in Figure S1A and S1B. In unadjusted analyses, increases in peak troponin ratio were strongly associated with each outcome up to 3×ULN; beyond this, the risk of ischemic events remained relatively constant as peak troponin ratios increased. Results were consistent after adjustment for baseline characteristics, except that the association with cardiovascular death was no longer significant. Note, the upper segment of the troponin linear spline (ratios >3×ULN) is not presented in Table 3 as all associations with outcomes are nonsignificant.

Table 3 also shows that there were no statistically significant interactions between peak troponin ratio and study treatment for any of the ischemic outcomes. The graphic representation of this relationship is displayed in Figure S2. In a subgroup analysis assessing this relationship among patients with angiographically proven coronary disease, the interaction between peak troponin ratio, study treatment, and either combined end point or all-cause mortality also lacked statistical significance. These results remained unchanged after adjustment for time from patient presentation to administration of study drug.

Peak Troponin and Platelet Function

Among patients enrolled in the TRILOGY ACS Platelet Function Substudy, 1810 (70.6%) had necessary measurements to

Table 1. Baseline Characteristics According to 48-Hour Peak Troponin Level

	Peak Troponin Level as Ratio of ULN				
	<1x (N=1574)	1x to <3x (N=1203)	3x to <5x (N=581)	≥5x (N=3405)	*P* Value
Demographics					
Age, y	65.0 (58.0, 72.0)	67.0 (58.0, 75.0)	67.0 (60.0, 75.0)	67.0 (60.0, 76.0)	<0.001
Age ≥75 y	285/1574 (18.1%)	301/1203 (25.0%)	156/581 (26.9%)	954/3405 (28.0%)	<0.001
Weight, kg	75.0 (65.0, 86.0)	75.0 (65.0, 89.0)	75.0 (65.0, 86.0)	77.0 (66.0, 89.0)	0.008
Weight <60 kg	211/1573 (13.4%)	191/1201 (15.9%)	78/581 (13.4%)	426/3401 (12.5%)	0.033
Sex					0.004
Female	648/1574 (41.2%)	466/1203 (38.7%)	223/581 (38.4%)	1221/3405 (35.9%)	
Male	926/1574 (58.8%)	737/1203 (61.3%)	358/581 (61.6%)	2184/3405 (64.1%)	
Region					<0.001
Central/Eastern Europe	714/1574 (45.4%)	354/1203 (29.4%)	195/581 (33.6%)	798/3405 (23.4%)	
East Asia	180/1574 (11.4%)	110/1203 (9.1%)	42/581 (7.2%)	246/3405 (7.2%)	
Indian subcontinent	147/1574 (9.3%)	140/1203 (11.6%)	43/581 (7.4%)	149/3405 (4.4%)	
Latin America	175/1574 (11.1%)	142/1203 (11.8%)	61/581 (10.5%)	381/3405 (11.2%)	
Mediterranean basin	103/1574 (6.5%)	86/1203 (7.1%)	32/581 (5.5%)	318/3405 (9.3%)	
North America	132/1574 (8.4%)	190/1203 (15.8%)	99/581 (17.0%)	821/3405 (24.1%)	
Western Europe/Scandinavia	112/1574 (7.1%)	158/1203 (13.1%)	95/581 (16.4%)	604/3405 (17.7%)	
Rest of world	11/1574 (0.7%)	23/1203 (1.9%)	14/581 (2.4%)	88/3405 (2.6%)	
Presentation characteristics					
Hours from presentation to start of study drug	83.3 (45.5, 141.4)	109.0 (64.8, 159.2)	109.7 (69.2, 158.4)	118.0 (72.3, 165.8)	<0.001
Killip class II–IV on presentation	129/1572 (8.2%)	148/1202 (12.3%)	81/581 (13.9%)	467/3404 (13.7%)	<0.001
Disease classification					<0.001
Unstable angina/unknown	1291/1574 (82.0%)	165/1203 (13.7%)	0/581 (0.0%)	0/3405 (0.0%)	
NSTEMI	283/1574 (18.0%)	1038/1203 (86.3%)	581/581 (100.0%)	3405/3405 (100.0%)	
Medical history					
Family history of CAD	421/1402 (30.0%)	361/1070 (33.7%)	162/522 (31.0%)	1064/2984 (35.7%)	0.002
Hypertension	1347/1570 (85.8%)	991/1201 (82.5%)	491/581 (84.5%)	2720/3393 (80.2%)	<0.001
Hyperlipidemia	925/1482 (62.4%)	711/1164 (61.1%)	334/565 (59.1%)	2175/3304 (65.8%)	0.001
Diabetes mellitus	598/1574 (38.0%)	488/1201 (40.6%)	244/581 (42.0%)	1309/3396 (38.5%)	0.214
Current/recent smoking*	268/1558 (17.2%)	231/1192 (19.4%)	119/573 (20.8%)	826/3363 (24.6%)	<0.001
Prior MI	697/1566 (44.5%)	559/1194 (46.8%)	260/576 (45.1%)	1408/3366 (41.8%)	0.016
Prior PCI	521/1569 (33.2%)	422/1196 (35.3%)	176/578 (30.4%)	795/3372 (23.6%)	<0.001
Prior CABG	261/1572 (16.6%)	218/1203 (18.1%)	90/580 (15.5%)	632/3390 (18.6%)	0.149
Prior PAD	92/1552 (5.9%)	89/1175 (7.6%)	43/572 (7.5%)	302/3333 (9.1%)	0.002
Prior atrial fibrillation	126/1533 (8.2%)	106/1175 (9.0%)	50/565 (8.8%)	263/3296 (8.0%)	0.685
Prior heart failure	304/1565 (19.4%)	178/1194 (14.9%)	98/576 (17.0%)	400/3376 (11.8%)	<0.001
Prior stroke	7/1571 (0.4%)	4/1198 (0.3%)	4/578 (0.7%)	24/3385 (0.7%)	0.414

Continued

Table 1. Continued

	Peak Troponin Level as Ratio of ULN				
	<1x (N=1574)	1x to <3x (N=1203)	3x to <5x (N=581)	≥5x (N=3405)	*P* Value
Baseline risk assessment					
GRACE risk score	116.0 (101.0, 130.0)	122.0 (106.0, 141.0)	128.0 (112.0, 147.0)	124.0 (108.0, 144.0)	<0.001
Body mass index, kg/m^2	27.0 (24.5, 30.5)	27.2 (24.2, 31.0)	27.2 (24.6, 30.8)	27.3 (24.4, 30.8)	0.485
Systolic blood pressure, mm Hg	130.0 (120.0, 140.0)	130.0 (117.0, 140.0)	126.0 (118.0, 138.0)	125.0 (115.0, 138.0)	<0.001
Heart rate, bpm	68.5 (62.0, 76.0)	69.0 (62.0, 76.0)	68.0 (60.0, 76.0)	69.0 (62.0, 76.0)	0.491
Hemoglobin, g/dL	13.6 (12.6, 14.6)	13.4 (12.3, 14.5)	13.6 (12.4, 14.7)	13.5 (12.4, 14.7)	0.104
Serum creatinine, mg/dL	1.0 (0.8, 1.1)	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)	<0.001
At randomization					
Treatment					0.323
Prasugrel	767/1574 (48.7%)	585/1203 (48.6%)	276/581 (47.5%)	1725/3405 (50.7%)	
Clopidogrel	807/1574 (51.3%)	618/1203 (51.4%)	305/581 (52.5%)	1680/3405 (49.3%)	
Clopidogrel strata					<0.001
No clopidogrel	123/1574 (7.8%)	36/1203 (3.0%)	22/581 (3.8%)	92/3405 (2.7%)	
Clopidogrel started in hospital ≤72 hours	905/1574 (57.5%)	798/1203 (66.3%)	421/581 (72.5%)	2759/3405 (81.0%)	
Home clopidogrel	546/1574 (34.7%)	369/1203 (30.7%)	138/581 (23.8%)	554/3405 (16.3%)	
Prerandomization procedures					
Angiography performed	555/1574 (35.3%)	568/1203 (47.2%)	256/581 (44.1%)	1941/3405 (57.0%)	<0.001
Concomitant medications at randomization					
Aspirin daily dose					
<100 mg	470/1574 (29.9%)	406/1203 (33.7%)	182/581 (31.3%)	1116/3405 (32.8%)	0.112
100 to 250 mg	943/1574 (59.9%)	628/1203 (52.2%)	308/581 (53.0%)	1658/3405 (48.7%)	<0.001
>250 mg	86/1574 (5.5%)	89/1203 (7.4%)	56/581 (9.6%)	396/3405 (11.6%)	<0.001
β-Blocker	1248/1574 (79.3%)	947/1203 (78.7%)	468/581 (80.6%)	2753/3405 (80.9%)	0.339
ACE-I/ARB	1173/1574 (74.5%)	883/1203 (73.4%)	446/581 (76.8%)	2635/3405 (77.4%)	0.018
Statin	1287/1574 (81.8%)	1016/1203 (84.5%)	482/581 (83.0%)	2945/3405 (86.5%)	<0.001
Proton pump inhibitor	355/1574 (22.6%)	308/1203 (25.6%)	185/581 (31.8%)	982/3405 (28.8%)	<0.001

Data presented as n/N (%) or median (25th, 75th percentile). ACE-I/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; bpm, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; ULN, upper limit of normal.
*Smoking within 30 days of randomization.

compute peak troponin/ULN ratios. Baseline characteristics by peak troponin ratio category are shown in Table S6. Compared with other groups, patients with peak troponin ratios <1xULN were younger, more often from Central/Eastern Europe, and less likely to be current/prior smokers or have a family history of coronary artery disease or hyperlipidemia. Additionally, they were less likely to have undergone angiography prior to randomization. Diabetes mellitus prevalence was similar across groups.

As displayed in Figure 2, there was no relationship between peak troponin and PRU among patients with angiographically proven coronary artery disease. Results remain unchanged even after adjustment for age group (≥75 years versus <75 years), clopidogrel stratum at randomization, randomized treatment assignment, and time from patient presentation to start of study drug.

Discussion

This analysis of TRILOGY ACS demonstrated that among NSTE ACS patients selected for medical management, including dual antiplatelet therapy with a P2Y12 antagonist, there was a graded relationship of increasing peak troponin with long-term ischemic events. Event rates at 30 months for patients with troponin ≥5×ULN were more than twice those for patients with peak troponin <1×ULN. There was no apparent

Table 2. Thirty-Month Ischemic Event Rates According to 48-Hour Peak Troponin Level

	Peak Troponin Level as Ratio of ULN				
	<1x (n=1574)	1x to <3x (n=1203)	3x to <5x (n=581)	≥5x (n=3405)	*P* Value*
Cardiovascular death, MI, or stroke					<0.001
No. of events	118	172	104	607	
KM event rate (95% CI)	11.3 (9.1–13.5)	18.4 (15.3–21.4)	26.6 (20.9–32.3)	25.1 (23.0–27.1)	
Cardiovascular death					<0.001
No. of events	62	80	41	297	
KM event rate (95% CI)	5.8 (4.2–7.3)	9.6 (7.0–12.3)	10.8 (6.6–15.0)	12.8 (11.1–14.4)	
Myocardial infarction					<0.001
No. of events	63	102	72	364	
KM event rate (95% CI)	6.4 (4.6–8.1)	10.4 (8.4–12.4)	17.6 (13.1–22.0)	15.6 (13.8–17.3)	
Cardiovascular death or MI					<0.001
No. of events	111	157	97	569	
KM event rate (95% CI)	10.6 (8.5–12.8)	16.8 (13.8–19.8)	25.0 (19.4–30.6)	23.5 (21.4–25.5)	
Stroke					0.005
No. of events	11	22	8	67	
KM event rate (95% CI)	1.2 (0.4–2.0)	2.8 (1.5–4.1)	1.8 (0.5–3.2)	3.3 (2.4–4.3)	
All-cause death					<0.001
No. of events	83	102	60	362	
KM event rate (95% CI)	7.3 (5.7–9.0)	11.8 (9.1–14.5)	14.7 (10.3–19.0)	14.8 (13.2–16.5)	

KM indicates Kaplan–Meier; MI, myocardial infarction; No., number; ULN, upper limit of normal.
*Two-sided *P* value based on the log-rank test.

incremental benefit of treatment with prasugrel versus clopidogrel according to peak troponin ratio among medically managed patients with NSTE ACS.

Peak Troponin and Long-Term Outcomes

Since the introduction of troponin testing in the early 1990s, its role has evolved from MI diagnosis to include risk stratification following ACS. It is known from previous analyses, including FRISC (Fragmin during Instability in Coronary Artery Disease) and TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18) that patients with NSTE ACS who have troponin elevations above the ULN at admission are at higher risk for death and recurrent ischemic events.[2,8,9] Furthermore, through additional analyses of trials such as GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) IIa, there is a well-characterized relationship between the magnitude of troponin elevation and outcomes among patients with NSTE ACS.[1] Troponin elevation can also identify which patients are most likely to benefit from aggressive antithrombotic therapy and an early invasive strategy.[8,9]

Recently, a secondary analysis of the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial, a study designed to examine the effect of vorapaxar (a protease-activated receptor-1 antagonist) versus placebo in NSTE ACS, identified a differential relationship between the magnitude of troponin elevation and 2-year mortality among patients treated with and without revascularization. In a subset of patients included in TRACER who did not undergo revascularization, increasing levels of peak cardiac troponin were associated with increasing long-term mortality (P=0.001). This relationship was not observed in those who underwent revascularization (P=0.23).[10]

The graded relationship of increasing peak troponin with ischemic events that we observed was consistent with this observation and prior studies evaluating troponin elevation as a prognostic indicator among patients with NSTE ACS. However, TRILOGY ACS provided the unique opportunity to establish this relationship over a long-term (30-month) follow-up period among patients who were medically managed with P2Y12 inhibitor therapy. Thus, the results of this analysis extend our understanding of the relationship of troponin with risk to long-term follow-up in the important population of medically managed NSTE ACS patients in the contemporary

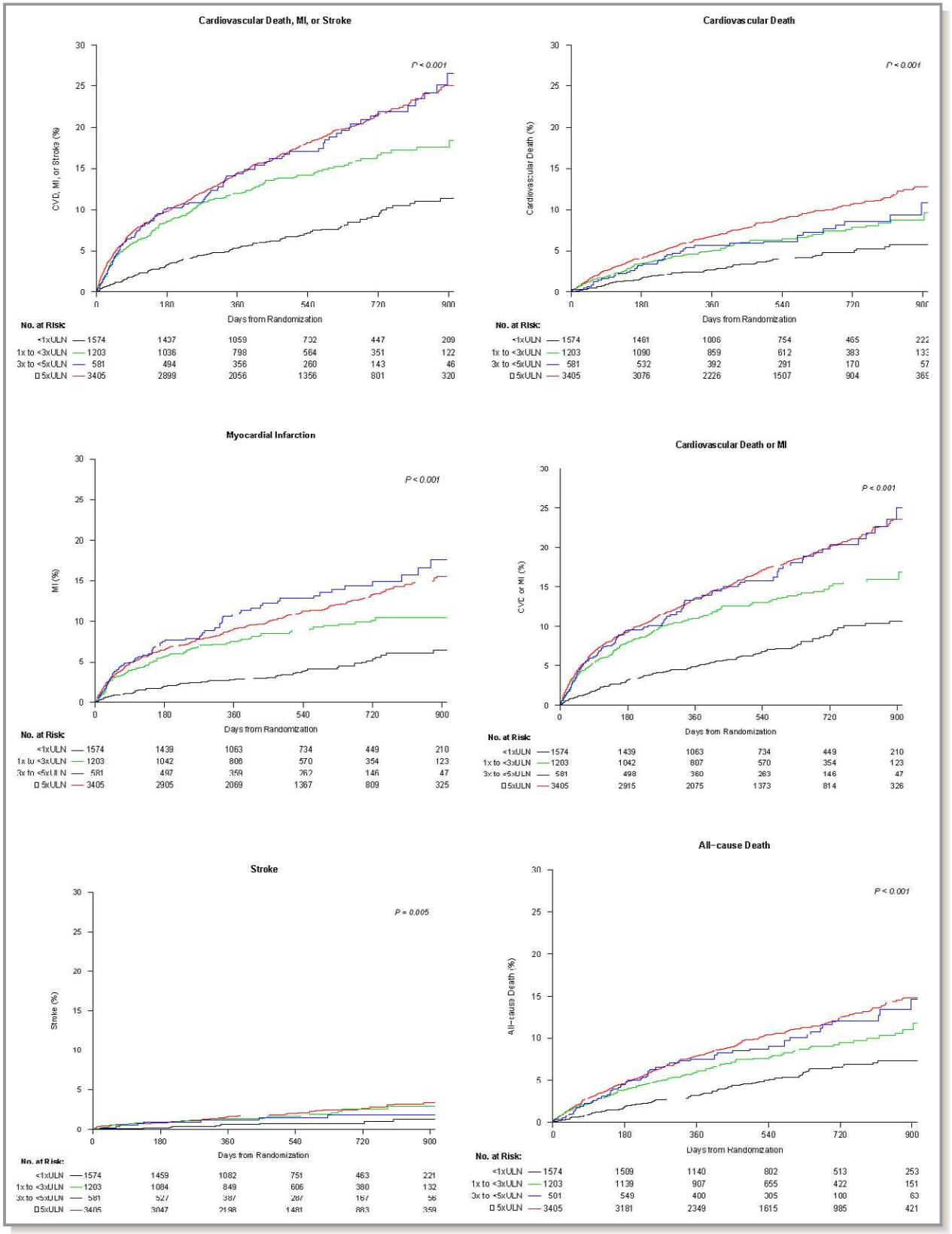

Figure 1. Cumulative Kaplan–Meier estimates of 30-month ischemic outcomes by 48-hour peak troponin elevation. For visualization of the numerical results presented in Table 2, Kaplan–Meier failure curves are presented for each efficacy end point. See Table 2 for relevant log-rank *P* values. MI indicates myocardial infarction; ULN, upper limit of normal.

Table 3. Unadjusted and Adjusted Hazard Ratios for 30-Month Ischemic Outcomes According to 48-Hour Peak Troponin Elevation

	Unadjusted HR (95% CI)*	Adjusted HR (95% CI)*	Peak Troponin×Treatment Interaction *P* Value
Cardiovascular death, MI, stroke	1.350 (1.263–1.442)	1.182 (1.066–1.311)	0.483
Cardiovascular death or MI	1.347 (1.257–1.443)	1.183 (1.062–1.318)	0.433
Cardiovascular death	1.291 (1.175–1.419)	1.090 (0.942–1.263)	0.371
Myocardial infarction	1.411 (1.292–1.541)	1.238 (1.081–1.419)	0.413
Stroke	1.387 (1.136–1.695)	0.998 (0.996–1.001)†	0.191
All-cause mortality	1.282 (1.179–1.393)	1.001 (1.000–1.001)†	0.234

HR indicates hazard ratio; MI, myocardial infarction.
*Per 1 unit increase in peak troponin/upper limit of normal ratio.
†Peak troponin elevation modeled linearly as the assumption of linearity was satisfied.

era of more potent P2Y12 inhibitor therapy. Our analyses demonstrate that despite advances in other medical therapy acutely and in secondary prevention, higher peak troponin values portend worse ischemic outcomes.

Peak Troponin and Effect of More Potent Antiplatelet Therapy

Substudies of several randomized clinical trials showed that the treatment effect of glycoprotein IIb/IIIa antagonists was amplified among patients with baseline troponin elevation, but there was no evident benefit among those without.[11–13] These findings were consistent across studies despite significant differences in patient populations, highlighting the importance of troponin elevation in identifying high-risk patients who may benefit from more potent antiplatelet therapy.[11] Given these observations and our results correlating troponin and rates of adverse cardiovascular events, it might be anticipated that higher-risk medically managed patients with greater peak troponin levels would also benefit preferentially from more potent antiplatelet therapy. However, we observed no such interaction of peak troponin level with more potent dual antiplatelet therapy among patients assigned to prasugrel compared with clopidogrel. This was consistent among the subset of patients with angiographically proven coronary disease who were medically managed in TRILOGY ACS. Thus, it is unlikely that inclusion of patients with troponin elevation unrelated to atherosclerotic coronary disease significantly influenced our analysis.

A number of considerations may contribute to our observations. Because this is a secondary analysis, it was not powered to detect an effect of more potent P2Y12 inhibition according to peak troponin values. Further, whereas the PARAGON-B (Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network B) study assessed a glycoprotein IIb/IIIa inhibitor (steady-state platelet aggregation inhibition >90%) versus placebo, neither prasugrel (50%) nor clopidogrel (30%) achieve that level of platelet aggregation inhibition, and they were compared head-to-head instead of against placebo.[14,15] Together these features of trial design may have contributed to the differential findings. Additionally, participants in TRILOGY ACS were randomized to prasugrel or clopidogrel ≈4.5 days after their index clinical event and could be enrolled up to 10 days after the index event.[5] It is possible that the benefit of more potent antiplatelet therapy may be related to the timing of therapy initiation relative to myocardial ischemia onset (which was much earlier in PARAGON-B), and particularly that patients with completed infarction by this time point may not benefit from more potent antiplatelet therapy. Additionally, prior evaluations of more potent antiplatelet therapies primarily focused on patients who underwent an invasive treatment strategy. It is possible that the benefit of more potent antiplatelet therapy seen in prior studies may have been derived from reduced periprocedural adverse ischemic outcomes. Finally, it is possible that bleeding complications may have attenuated the benefit of more potent antiplatelet therapy.

Peak Troponin and Platelet Reactivity

A substudy of TRILOGY ACS evaluated the effects of prasugrel and clopidogrel on serial PRU assessments. This analysis revealed lower platelet reactivity with prasugrel compared with clopidogrel; however, there was no difference in ischemic outcomes by treatment assignment.[4,5] Our exploratory analysis of the TRILOGY ACS Platelet Function Substudy revealed that the effect of treatment on platelet inhibition (as assessed by 30-day PRU values) did not vary substantially based on peak troponin value.

Strengths and Limitations

This secondary analysis of TRILOGY ACS demonstrates a novel correlation between troponin elevation and prognosis in a study sample selected for medical management of NSTE ACS. One of the strengths of our analysis is that it used data

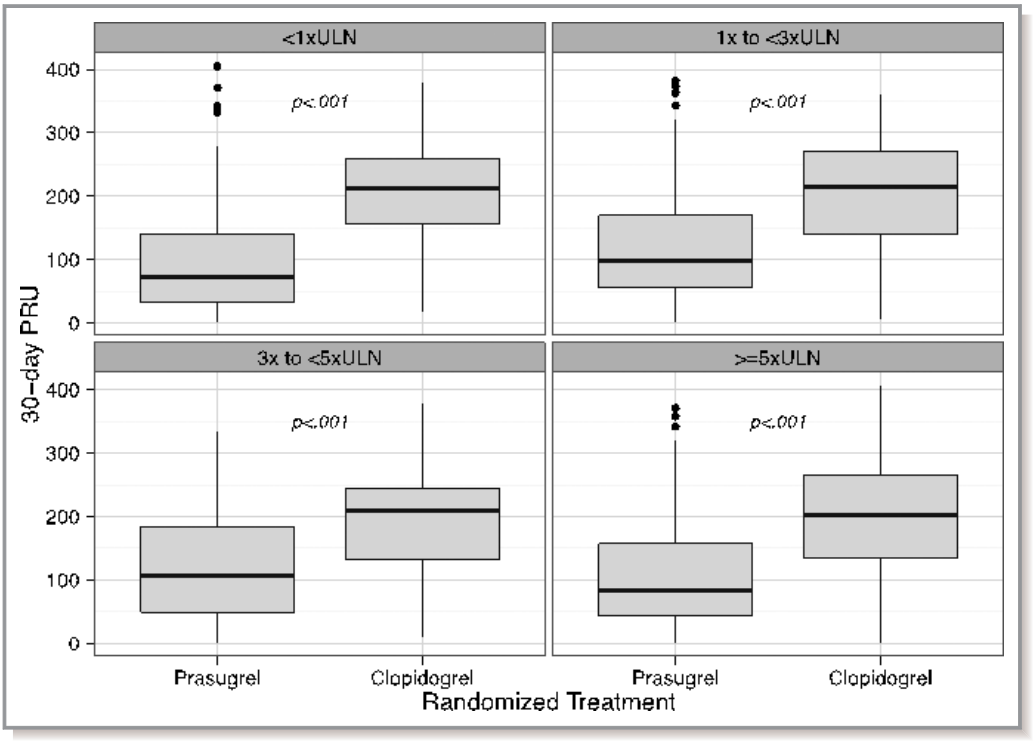

Figure 2. Forty-eight-hour peak troponin ratio and 30-day platelet reactivity unit (PRU). For patients enrolled in the Platelet Function Substudy, a box plot is used to assess the unadjusted association of peak troponin elevation with 30-day PRU, as well as the interaction with study treatment (P<0.001). ULN indicates upper limit of normal.

collected as part of a large, multinational, randomized trial, which enhances data consistency and eliminates bias in the assessment of overall treatment effects. Because of the large number of subjects, the results are statistically robust. However, because these results are drawn from a patient population selected for a randomized clinical trial, they may not be generalizable to the broader population of medically managed patients in general practice. Troponin values used for our analysis were collected up to 48 hours after presentation, consistent with contemporary clinical practice. It is possible that by limiting our analysis to values within 48 hours of presentation, a higher peak value could have been missed, but this rule was applied consistently to all patients. Peak troponin data within 48 hours were not available in about 25% of study participants, eliminating this group from our analysis. Although there were differences between those included or not, most were modest and would not be expected to alter the relationships we observed (Table S5). Troponin assays were not standardized across participating sites. Thus, they reflect a wide variety of individual assays with variable assay performance characteristics, and potentially varying site-specific ULNs for the same assay. However, this reflects the state of actual clinical practice, and we attempted to account for this by normalizing the reported values using a ratio of the reported value to the ULN reported for the assay. This variability and resultant "noise" introduced would be expected to result in an underestimation of the relationship between increasing troponin level and outcomes. Additionally, it is possible that some patients with elevated troponin levels who were included in TRILOGY ACS did not have significant coronary artery disease. In this case, the true association of troponin with long-term ischemic outcomes may have been underestimated. Of the patients who underwent angiography, however, very few had absence of obstructive coronary disease, and when we excluded those patients from our analyses, there were no differences in our findings. Although designed to evaluate medically managed patients, a small number of patients (7.1%) underwent postindex revascularization at a median of 120.5 days after the index event. Because of the infrequency of downstream revascularization in our study sample and that it occurred late relative to the time of troponin sampling, we believe the commitment to an initial medical management strategy was met and that it is unlikely that our results were significantly affected. Finally, it is possible that because we defined peak troponin using values collected within 48 hours after the index event, the true peak troponin value was missed. However, it is important to note that the impact of missing the true peak would tend to underestimate the relationship between peak troponin level

and adverse outcomes. Despite its limitations, our analysis shows the prognostic importance of higher levels of troponin for long-term outcomes among medically managed patients with NSTE ACS, even in the setting of treatment with modern, potent antiplatelet agents, and the effect is not related to the degree of platelet inhibition as assessed by the P2Y12 assay.

Conclusion

Among NSTE ACS patients selected for medical management, there was a graded relationship of increasing peak troponin with long-term ischemic events, but no heterogeneity of treatment effect for prasugrel versus clopidogrel (clinical or PRU-based) according to 48-hour peak troponin level.

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Disclosures

Newby has reported all potential conflicts at https://www.dcri.org/about-us/conflict-of-interest. Lüscher reports grants from AstraZeneca and from Eli Lilly during the conduct of the study. White reports grants from Sanofi Aventis, Eli Lilly and Company, National Institute of Health, and Merck Sharpe & Dohm, grants and personal fees from AstraZeneca, grants from GlaxoSmithKline, Omthera Pharmaceuticals, Pfizer New Zealand, Intarcia Therapeutics Inc., Elsai Inc., DalGen Products and Services, and Daiichi Sankyo Pharma Development, outside the submitted work. Ohman reports receiving grant support and travel expenses from Daiichi Sankyo and Eli Lilly, consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Liposcience, Merck, Pozen, Hoffmann-La Roche, Sanofi-Aventis, The Medicines Company, and Web MD; grant support from Gilead Sciences; and lecture fees from Gilead Sciences, Boehringer Ingelheim, and The Medicines Company. Roe reports research grants from Eli Lilly and Company, Janseen Pharmaceuticals, Sanofi-Aventis, Daiichi-Sankyo, Familial Hypercholesterolemia Foundation, and Ferring Pharmaceuticals; educational activities or lectures for Amgen and Bristol-Myers Squibb; consulting or other services for AstraZeneca, Eli Lilly and Company, Merck & Co., Elsevier Publishers, Amgen, Boehringer-Ingelheim, and PriMed. All conflicts of interest are listed at https://www.dcri.org/about-us/conflict-of-interest. Hamm reports personal fees from GSK, during the conduct of the study; and personal fees from BRAHMS, outside the submitted work. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Data S1.

TRILOGY ACS Adjustment Models

TRILOGY ACS Efficacy Adjustment Models

The TRILOGY ACS efficacy outcome adjustment models were constructed using a comprehensive list of patient characteristics and risk factors selected based on clinical knowledge (for a complete list, see the table below). Missing values were imputed using a multiple imputation approach that applies an MCMC method to create a monotone missing pattern and then uses a multivariate normal distribution to impute missing values. The imputation method replaces each missing value with a representative sample of plausible values by creating *m* complete data sets. As a result, the uncertainty due to the missingness is appropriately accounted for and analyses on the imputed data result in valid statistical inference. The *m* complete data sets can be analyzed using standard statistical procedures; the results are then aggregated across all simulated data sets. In this work, *m* was taken to be 25. Because a comparison of descriptive statistics from the first complete data set and the aggregation of the 25 complete data sets revealed negligible differences, only the first complete data set was used when fitting the adjustment for ease of computation. When fitting the adjustment model, the proportional hazards assumption was checked for each covariate and the linearity assumption was checked for each continuous covariate at alpha-level 0.05. If the proportional hazard assumption was violated, an interaction of the variable with log-transformed time was included in the model. If the linearity assumption was violated, a restricted cubic spline was used to approximate the non-linear relationship of the variable with the outcome. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and R 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table S4 details the composition of each adjustment model.

TRILOGY ACS Bleeding Adjustment Models

The TRILOGY ACS bleeding outcome adjustment models were constructed using a comprehensive list of patient characteristics and risk factors selected based on clinical knowledge (for a complete list, see Table S4). Missing values were imputed using a multiple imputation approach that applies an MCMC method to create a monotone missing pattern and then uses a multivariate normal distribution to impute missing values. The imputation method replaces each missing value with a representative sample of plausible values by creating *m* complete data sets. As a result, the uncertainty due to the missingness is appropriately accounted for and analyses on the imputed data result in valid statistical inference. The *m* complete data sets can be analyzed using standard statistical procedures; the results are then aggregated across all simulated data sets. In this work, *m* was taken to be 25. Because a comparison of descriptive statistics from the first complete data set and the aggregation of the 25 complete data sets revealed negligible differences, only the first complete data set was used when fitting the adjustment for ease of computation. When fitting the adjustment model, the proportional hazards assumption was checked for each covariate and the linearity assumption was checked for each continuous covariate at alpha-level 0.05. If the proportional hazard assumption was violated, an interaction of the variable with time was included in the model. If the linearity assumption was violated, a restricted cubic spline was used to approximate the non-linear relationship of the variable with the outcome. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria)

Table S1. Censoring scheme for the primary endpoint (cardiovascular death, myocardial infarction, or stroke) and for nonfatal secondary endpoints

Scenario	**Censoring Rule**
Completed final study visit	Final visit date (date of study termination / last contact on end-of-study case report form page unless type of visit = 95)
Death during follow-up	Adjudicated death date
Withdrew consent	Date withdrew consent
No final visit and did not withdraw consent	Last onsite or telephone visit date
Vital status only alive	Last onsite or telephone visit date
Vital status only died	Last onsite or telephone visit date

Table S2. Censoring scheme for cardiovascular death or for all-cause death

Scenario	**Censoring Rule**
Completed final study visit	Final visit date (date of study termination / last contact on end-of-study page unless type of visit = 95)
Death during follow-up	Adjudicated death date
Withdrew consent	Date withdrew consent
No final visit and did not withdraw consent	Last date when vital status is known
Vital status only alive	Last date when vital status is known
Vital status only died (without adjudication of a COD)	Death date (if available)
Vital status only died (with adjudication of a COD)	Adjudicated death date

Table S3. Descriptive statistics for troponin

	Troponin I	**Troponin T**	**Troponin**
N	4796	2185	6763
Median time (Q1, Q3) from initial to peak sample value*	11.25 (7.00, 16.98)	11.88 (7.00, 19.42)	11.36 (7.00, 17.55)
Peak ratio percentiles			
100% Max	448222.22	6000.00	448222.22
99%	1082.00	318.18	900.00
98%	609.75	237.86	506.25
97%	462.10	165.00	362.22
96%	351.00	132.14	290.00
95%	293.25	116.00	240.00
90%	143.00	59.46	115.67
75% Q3	36.45	17.60	28.90
50% Median	5.50	3.57	5.00
25% Q1	1.10	0.90	1.00
0% Min	<0.01	<0.01	<0.01

*Time (in hours) from initial to peak sample value within 48 hours after index presentation. Calculated from samples with non-missing initial and peak date/times.

Table S4. TRILOGY ACS Efficacy and Bleeding Adjustment Models

Characteristic	CVD/MI/Stroke	CVD	MI	Stroke	All-Cause Death	GUSTO Severe / LT / Moderate Bleeding (non-CABG)	TIMI Major/ Minor Bleeding (non-CABG)
Randomized Treatment	✓	✓	✓	✓	✓	-	-
Weight (kg)	✓	✓	✓	✓	✓	✓	✓
Age (y)	✓	✓	✓	✓	✓	✓*	✓*
Female sex	✓	✓	✓	✓	✓	✓	✓
NSTEMI	✓	✓	✓	✓	✓	✓	✓
Killip class I on presentation	✓	✓	✓	✓	✓	✓	✓
Time from presentation to study drug start (h)	✓	✓	✓	✓	✓	✓	✓
Cardiovascular risk factors:							
Family history of CAD	✓	✓	✓	✓	✓	-	-
Hypertension	✓	✓	✓	✓	✓	-	-
Hyperlipidemia	✓	✓	✓	✓	✓	-	-
Diabetes Mellitus	✓	✓	✓	✓	✓	-	-
Current/recent smoke	✓	✓	✓	✓	✓	-	-
Previous peptic ulcer disease	-	-	-	-	-	✓	✓
Cardiovascular disease history:							
Previous myocardial infarction	✓	✓	✓	✓	✓	-	-
Previous PCI	✓	✓	✓	✓	✓	-	-
Previous CABG	✓	✓	✓	✓	✓	-	-
Previous peripheral artery disease	✓	✓	✓	✓	✓	✓	✓
Previous atrial fibrillation	✓	✓	✓	✓	✓	-	-
Previous heart failure	✓	✓	✓	✓	✓	-	-
At randomization:							
Systolic blood pressure (mmHg)	✓*	✓	✓	✓*	✓	✓*	✓
Heart rate (bpm)	✓	✓	✓	✓*	✓	-	-
Heart rate*log(time)	✓	✓	-	-	✓	-	-
Clopidogrel stratum 2 – Started in hospital ≤72 h	✓	✓	✓	✓	✓	✓	✓

Characteristic	CVD/MI/Stroke	CVD	MI	Stroke	All-Cause Death	GUSTO Severe / LT / Moderate Bleeding (non-CABG)	TIMI Major/ Minor Bleeding (non-CABG)
Clopidogrel stratum 3 – At home	✓	✓	✓	✓	✓	✓	✓
Angiography performed?	✓	✓	✓	✓	✓	✓	✓
Hemoglobin (g/dL)	✓	✓	✓	✓	✓	✓	✓
Hemoglobin (g/dL)*(time)	-	-	-	-	-	✓	-
Creatinine (mg/dL)	✓*	✓	✓*	✓	✓	✓	✓
Baseline concomitant medications:							
Beta-blocker	✓	✓	✓	✓	✓	✓	✓
ACE/ARB	✓	✓	✓	✓	✓	-	-
Statin	✓	✓	✓	✓	✓	-	-
PPI	✓	✓	✓	✓	✓	-	-
Region:							
East Asia	✓	✓	✓	✓	✓	-	-
Indian Subcontinent	✓	✓	✓	✓	✓	-	-
Latin America	✓	✓	✓	✓	✓	-	-
Mediterranean Basin	✓	✓	✓	✓	✓	-	-
North America	✓	✓	✓	✓	✓	-	-
Rest of World	✓	✓	✓	✓	✓	-	-
Western Europe/Scandinavia	✓	✓	✓	✓	✓	-	-

*A restricted cubic spline was used to account for the non-linear relationship of the variable with the outcome.

Table S5. Baseline characteristics of included and excluded study patients

	Included (N=6763)	Excluded (N=2563)	P-value
Demographics			
Age, yrs	66.0 (59.0, 75.0)	64.0 (57.0, 71.0)	<0.001
Age ≥75 yrs	1696/6763 (25.1%)	387/2563 (15.1%)	<0.001
Weight, kg	76.0 (65.0, 88.0)	72.1 (62.0, 83.0)	<0.001
Weight <60 kg	906/6756 (13.4%)	495/2563 (19.3%)	<0.001
Female sex	2558/6763 (37.8%)	1092/2563 (42.6%)	<0.001
Region			<0.001
Central/Eastern Europe	2061/6763 (30.5%)	1029/2563 (40.1%)	
East Asia	578/6763 (8.5%)	174/2563 (6.8%)	
Indian Subcontinent	479/6763 (7.1%)	662/2563 (25.8%)	
Latin America	759/6763 (11.2%)	517/2563 (20.2%)	
Mediterranean Basin	539/6763 (8.0%)	119/2563 (4.6%)	
North America	1242/6763 (18.4%)	29/2563 (1.1%)	
Western Europe/Scandinavia	969/6763 (14.3%)	25/2563 (1.0%)	
Rest of World	136/6763 (2.0%)	8/2563 (0.3%)	
Presentation characteristics			
Hours from presentation to start of study drug	108.5 (65.5, 159.9)	105.1 (53.2, 157.4)	0.006
Killip class II–IV on presentation	825/6759 (12.2%)	310/2559 (12.1%)	0.904
Disease classification			<0.001
Unstable angina/unknown	1456/6763 (21.5%)	1350/2563 (52.7%)	
NSTEMI	5307/6763 (78.5%)	1213/2563 (47.3%)	
Medical history			
Family history of CAD	2008/5978 (33.6%)	510/2303 (22.1%)	<0.001
Hypertension	5549/6745 (82.3%)	2076/2558 (81.2%)	0.213
Hyperlipidemia	4145/6515 (63.6%)	1102/2355 (46.8%)	<0.001
Diabetes mellitus	2639/6752 (39.1%)	900/2554 (35.2%)	<0.001
Current/recent smoking*	1444/6686 (21.6%)	400/2542 (15.7%)	<0.001
Prior MI	2924/6702 (43.6%)	1063/2544 (41.8%)	0.110
Prior PCI	1914/6715 (28.5%)	511/2555 (20.0%)	<0.001
Prior CABG	1201/6745 (17.8%)	253/2558 (9.9%)	<0.001
Prior PAD	526/6632 (7.9%)	154/2523 (6.1%)	0.003
Prior atrial fibrillation	545/6569 (8.3%)	165/2532 (6.5%)	0.005
Prior heart failure	980/6711 (14.6%)	649/2554 (25.4%)	<0.001
Prior stroke	39/6732 (0.6%)	8/2555 (0.3%)	0.106
Baseline risk assessment			
GRACE risk score	122.0 (106.0, 140.0)	119.0 (103.0, 136.0)	<0.001
Body mass index, kg/m^2	27.2 (24.4, 30.8)	26.7 (23.8, 29.9)	<0.001
Systolic blood pressure, mmHg	128.0 (117.0, 139.0)	130.0 (120.0, 140.0)	<0.001
Heart rate, bpm	69.0 (61.0, 76.0)	70.0 (62.0, 78.0)	<0.001
Hemoglobin, g/dL	13.5 (12.4, 14.6)	13.6 (12.5, 14.7)	0.115
Serum creatinine, mg/dL	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	<0.001
At randomization			
Treatment			0.186
Prasugrel	3353/6763 (49.6%)	1310/2563 (51.1%)	
Clopidogrel	3410/6763 (50.4%)	1253/2563 (48.9%)	
Clopidogrel strata			<0.001
1 - No clopidogrel	273/6763 (4.0%)	125/2562 (4.9%)	
2 - Clopidogrel started in-hospital ≤72 hrs	4883/6763 (72.2%)	1630/2562 (63.6%)	
3 - Home clopidogrel	1607/6763 (23.8%)	807/2562 (31.5%)	
Pre-randomization procedures			
Angiography performed	3320/6763 (49.1%)	531/2562 (20.7%)	<0.001
Concomitant medications at randomization			
Aspirin daily dose			
<100 mg	2174/6763 (32.1%)	935/2563 (36.5%)	<0.001
100–250 mg	3537/6763 (52.3%)	1419/2563 (55.4%)	0.008
>250 mg	627/6763 (9.3%)	46/2563 (1.8%)	<0.001
Beta-blocker	5416/6763 (80.1%)	1835/2563 (71.6%)	<0.001
ACE-I/ARB	5137/6763 (76.0%)	1890/2563 (73.7%)	0.027
Statin	5730/6763 (84.7%)	2046/2563 (79.8%)	<0.001
Proton pump inhibitor	1830/6763 (27.1%)	514/2563 (20.1%)	<0.001

*Smoking within 30 days of randomization.
Data presented as n/N (%) or median (25^{th}, 75^{th} percentile).
ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; GRACE, Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention.

Table S6. Baseline characteristics according to 48-hour peak troponin level in Platelet Function Substudy participants

Characteristic	Peak troponin level as ratio of ULN				P-value
	<1x (N=468)	1x to <3x (N=325)	3x to <5x (N=158)	≥5x (N=856)	
Demographics					
Age, yrs	66.0 (58.5, 72.0)	67.0 (59.0, 75.0)	67.5 (60.0, 74.0)	66.0 (59.0, 74.0)	0.089
Age ≥75	85/468 (18.2%)	86/325 (26.5%)	39/158 (24.7%)	200/856 (23.4%)	0.034
Weight, kg	75.0 (65.0, 86.0)	78.0 (65.0, 90.0)	77.1 (67.0, 90.0)	75.0 (65.0, 87.1)	0.188
Weight <60 kg	64/468 (13.7%)	50/325 (15.4%)	15/158 (9.5%)	123/856 (14.4%)	0.344
Sex					0.096
Female	196/468 (41.9%)	132/325 (40.6%)	60/158 (38.0%)	303/856 (35.4%)	
Male	272/468 (58.1%)	193/325 (59.4%)	98/158 (62.0%)	553/856 (64.6%)	
Region					<0.001
Central/Eastern Europe	206/468 (44.0%)	93/325 (28.6%)	49/158 (31.0%)	144/856 (16.8%)	
East Asia	98/468 (20.9%)	53/325 (16.3%)	16/158 (10.1%)	134/856 (15.7%)	
Indian Subcontinent	50/468 (10.7%)	29/325 (8.9%)	8/158 (5.1%)	58/856 (6.8%)	
Latin America	23/468 (4.9%)	13/325 (4.0%)	17/158 (10.8%)	77/856 (9.0%)	
Mediterranean Basin	15/468 (3.2%)	8/325 (2.5%)	2/158 (1.3%)	26/856 (3.0%)	
North America	46/468 (9.8%)	69/325 (21.2%)	40/158 (25.3%)	284/856 (33.2%)	
Western Europe/Scandinavia	29/468 (6.2%)	47/325 (14.5%)	17/158 (10.8%)	83/856 (9.7%)	
Rest of World	1/468 (0.2%)	13/325 (4.0%)	9/158 (5.7%)	50/856 (5.8%)	
Presentation characteristics					
Hours from presentation to start of study drug	86.9 (44.8, 144.2)	102.3 (68.2, 151.6)	122.2 (73.5, 166.3)	120.2 (70.5, 169.1)	<0.001
Killip class II–IV on presentation	40/467 (8.6%)	37/325 (11.4%)	24/158 (15.2%)	117/856 (13.7%)	0.029
Disease classification					<0.001
Unstable angina/unknown	382/468 (81.6%)	41/325 (12.6%)	0/158 (0.0%)	0/856 (0.0%)	
NSTEMI	86/468 (18.4%)	284/325 (87.4%)	158/158 (100.0%)	856/856 (100.0%)	
Medical history					
Family history of CAD	108/395 (27.3%)	107/291 (36.8%)	58/140 (41.4%)	300/788 (38.1%)	0.001
Hypertension	391/465 (84.1%)	269/324 (83.0%)	142/158 (89.9%)	690/854 (80.8%)	0.036
Hyperlipidemia	224/414 (54.1%)	205/309 (66.3%)	96/147 (65.3%)	550/832 (66.1%)	<0.001
Diabetes mellitus	175/468 (37.4%)	136/325 (41.8%)	66/158 (41.8%)	319/855 (37.3%)	0.391
Current/recent smoking*	69/460 (15.0%)	61/321 (19.0%)	32/156 (20.5%)	226/848 (26.7%)	<0.001
Prior MI	200/467 (42.8%)	146/323 (45.2%)	69/155 (44.5%)	366/850 (43.1%)	0.897
Prior PCI	141/468 (30.1%)	118/323 (36.5%)	40/158 (25.3%)	202/852 (23.7%)	<0.001
Prior CABG	59/467 (12.6%)	56/325 (17.2%)	23/158 (14.6%)	155/854 (18.1%)	0.062
Prior PAD	14/463 (3.0%)	25/319 (7.8%)	13/156 (8.3%)	61/834 (7.3%)	0.007
Prior atrial fibrillation	57/452 (12.6%)	32/320 (10.0%)	12/153 (7.8%)	70/840 (8.3%)	0.078
Prior heart failure	117/462 (25.3%)	55/319 (17.2%)	24/156 (15.4%)	115/848 (13.6%)	<0.001
Prior stroke	2/467 (0.4%)	1/322 (0.3%)	3/157 (1.9%)	5/851 (0.6%)	0.203

Characteristic	Peak troponin level as ratio of ULN				P-value
	<1x (N=468)	1x to <3x (N=325)	3x to <5x (N=158)	≥5x (N=856)	
Baseline risk assessment					
GRACE risk score	118.0 (101.0, 134.0)	124.0 (106.0, 143.0)	130.0 (112.0, 144.0)	123.0 (108.0, 143.0)	<0.001
Body mass index, kg/m^2	26.7 (24.2, 30.5)	27.0 (24.1, 31.1)	27.5 (24.7, 32.0)	27.0 (24.2, 30.6)	0.235
Systolic blood pressure, mmHg	130.0 (120.0, 140.0)	130.0 (118.0, 140.0)	126.5 (115.0, 136.0)	124.0 (110.0, 135.0)	<0.001
Heart rate, bpm	68.0 (61.0, 75.0)	68.0 (60.0, 75.0)	68.0 (62.0, 77.0)	70.0 (62.0, 77.0)	0.061
Hemoglobin, g/dL	13.8 (12.8, 14.7)	13.4 (12.4, 14.5)	13.6 (12.5, 14.9)	13.6 (12.5, 14.7)	0.042
Serum creatinine, mg/dL	1.0 (0.8, 1.1)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	0.008
At randomization					
Treatment					0.577
Prasugrel	233/468 (49.8%)	158/325 (48.6%)	69/158 (43.7%)	423/856 (49.4%)	
Clopidogrel	235/468 (50.2%)	167/325 (51.4%)	89/158 (56.3%)	433/856 (50.6%)	
Clopidogrel strata					<0.001
1 - No clopidogrel	28/468 (6.0%)	9/325 (2.8%)	8/158 (5.1%)	33/856 (3.9%)	
2 - Clopidogrel started in-hospital ≤72 hrs	255/468 (54.5%)	217/325 (66.8%)	119/158 (75.3%)	686/856 (80.1%)	
3 - Home clopidogrel	185/468 (39.5%)	99/325 (30.5%)	31/158 (19.6%)	137/856 (16.0%)	
Pre-randomization procedures					
Angiography performed	136/468 (29.1%)	155/325 (47.7%)	77/158 (48.7%)	475/856 (55.5%)	<0.001
Concomitant medications at randomization					
Aspirin daily dose					
<100 mg	180/468 (38.5%)	156/325 (48.0%)	77/158 (48.7%)	342/856 (40.0%)	0.009
100–250 mg	242/468 (51.7%)	118/325 (36.3%)	58/158 (36.7%)	326/856 (38.1%)	<0.001
>250 mg	17/468 (3.6%)	23/325 (7.1%)	16/158 (10.1%)	119/856 (13.9%)	<0.001
Beta-blocker	363/468 (77.6%)	257/325 (79.1%)	116/158 (73.4%)	674/856 (78.7%)	0.479
ACE-I/ARB	330/468 (70.5%)	242/325 (74.5%)	118/158 (74.7%)	615/856 (71.8%)	0.566
Statin	367/468 (78.4%)	278/325 (85.5%)	132/158 (83.5%)	720/856 (84.1%)	0.028
Proton pump inhibitor	115/468 (24.6%)	81/325 (24.9%)	43/158 (27.2%)	215/856 (25.1%)	0.930

*Smoking within 30 days of randomization.

Data presented as n/N (%) or median (25th, 75th percentile).

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; GRACE, Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention.

Figure S1A. Estimated spline transformation and 95% confidence interval for the relationship of troponin elevation and unadjusted rates of cardiovascular death, MI, or stroke through 30 months

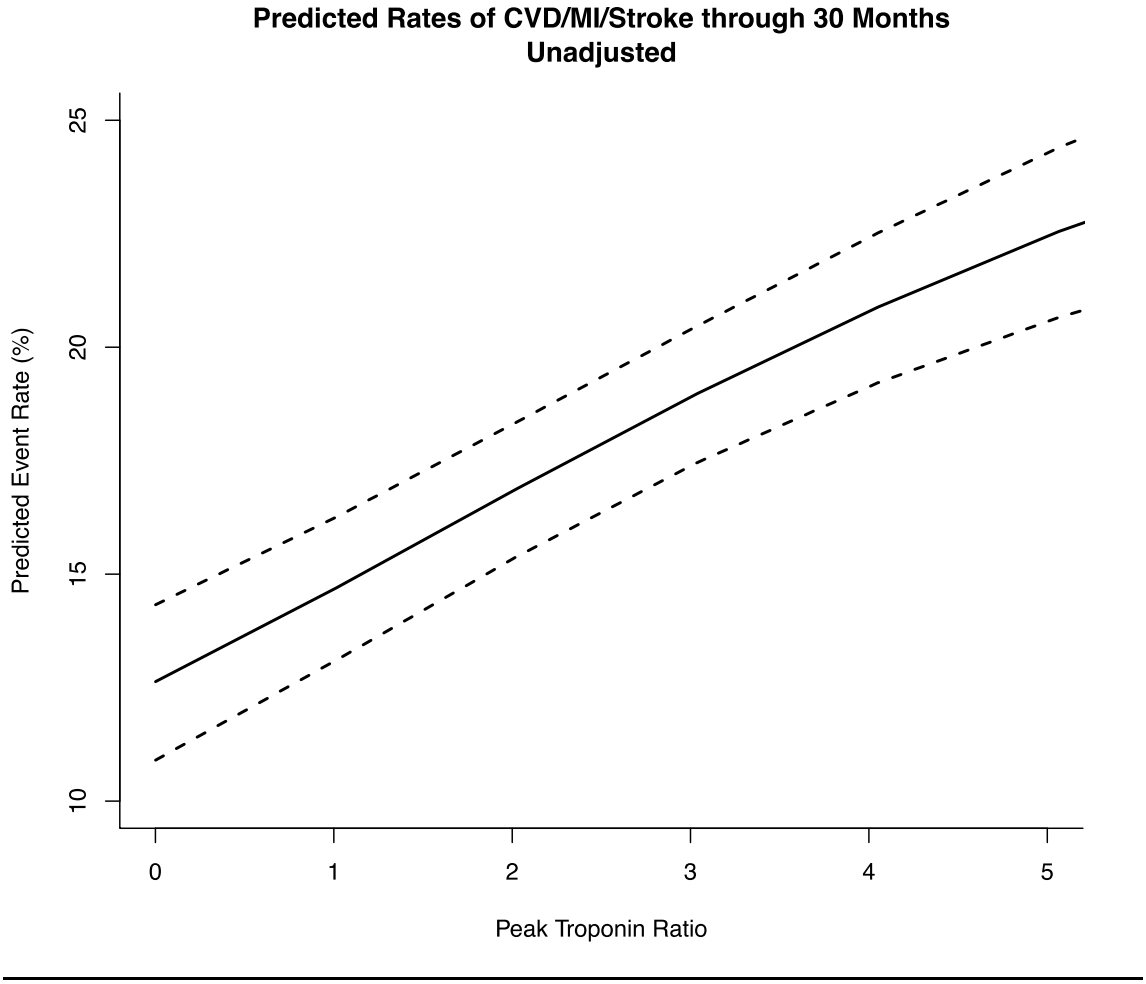


Figure S1B. Estimated spline transformation and 95% confidence interval for the relationship of troponin elevation and adjusted rates of cardiovascular death, MI, or stroke through 30 months

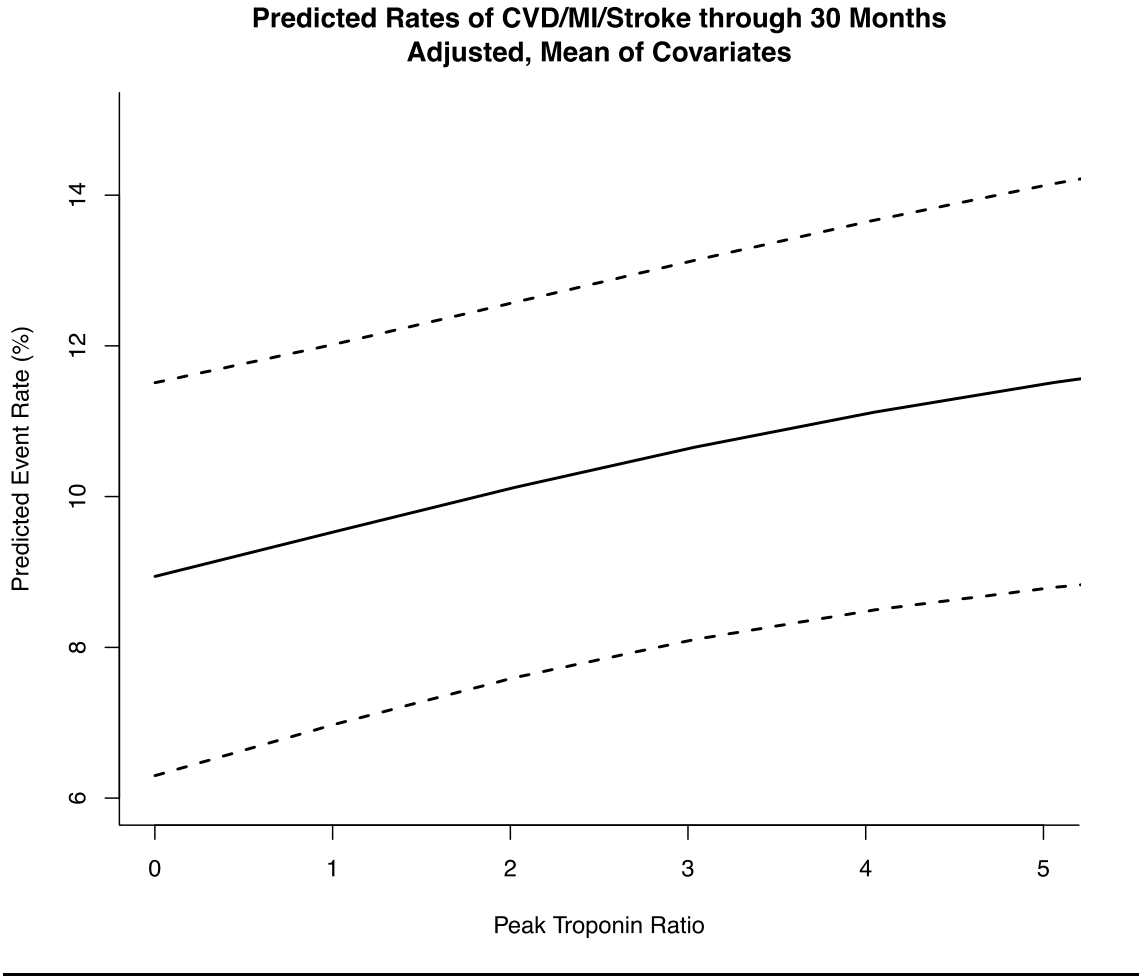
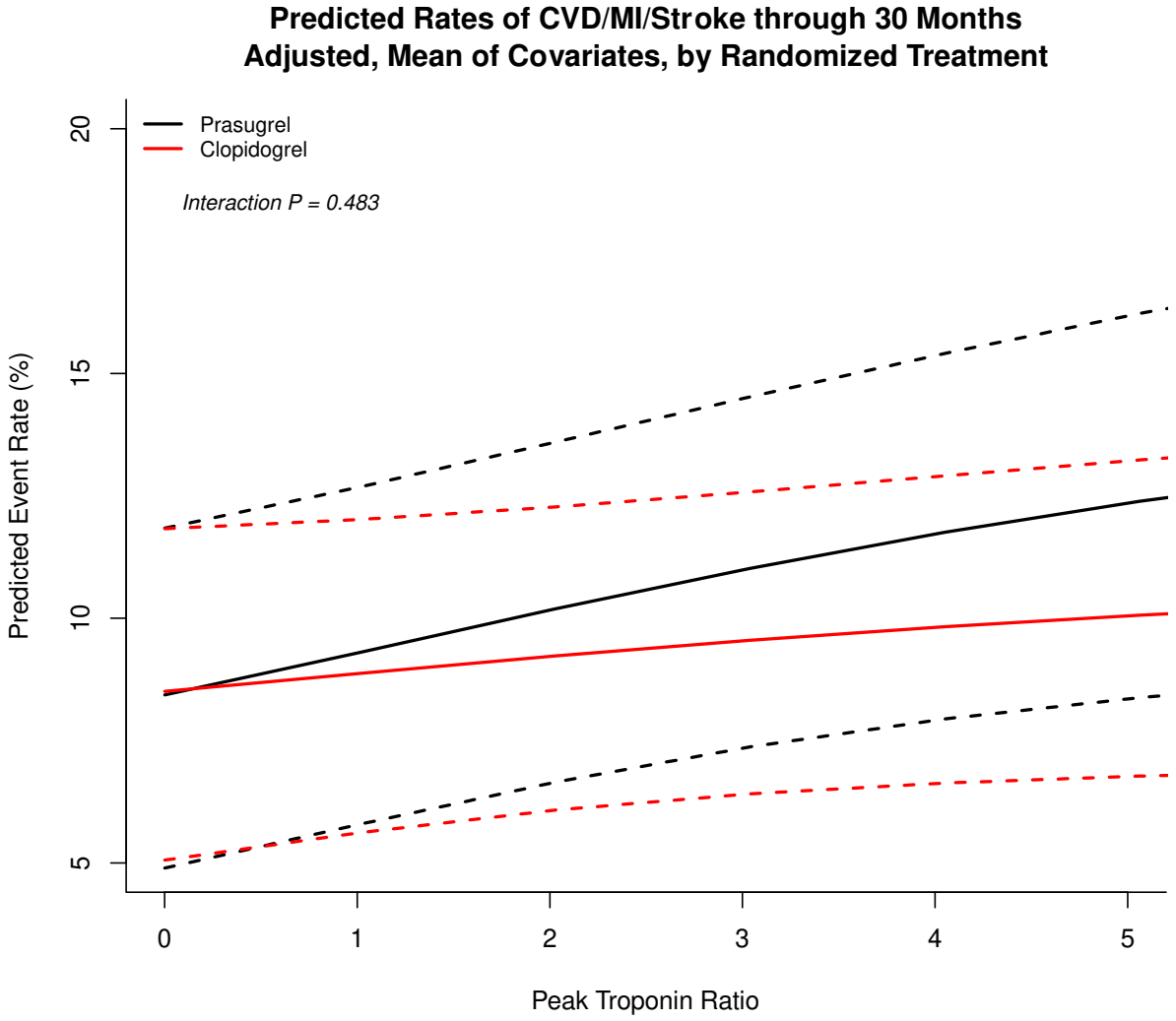


Figure S2. Estimated spline transformation and 95% confidence interval for the relationship of troponin elevation and adjusted rates of cardiovascular death, myocardial infarction, or stroke through 30 months stratified by treatment



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